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CONTRACTING ORGANIZATION: Cedars-Sinai Medial Center

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Traumatic optical neuropathy (TON) results from trauma to optic nerve by head and eye injuries to both military and civilian population such as accidents, and blast related combat trauma. TON leads to irreversible blindness and represent a major public health burden with both economical and social impacts. Unfortunately, treatment is still rather limited. A large body of evidence indicates that TON affects optic nerve and its target neurons in the central nervous system, which provide vital retrograde trophic support to optic nerve. We hypothesize that systemic administration of bone marrow derived mesenchymal stem cells (MSC) to treat traumatic optic neuropathy (TON) will preserve/repair optic nerve, stabilize the unstable environment due to trauma and promote RGC regeneration and outgrowth by promoting the release of paracrine and autocrine mediators; induced Schwann cells from MSC (M-Sch) will repair the damaged RGC by remyelinating and providing multiple trophic factors. We have used Long Evan (LE) rats as a model for TON, MSC were isolated from LE rats, M-Sch were induced from MSC. Our main findings: 1. Using our modified forceps, a reliable and reproducible TON model was created. 2. Rat MSC and M-Sch were reliable produced for experiments. 3. Systemic administration of MSC significantly preserved retinal ganglion cell survival after TON. 4. Systemic administration of MSC also promote limited RGC axons regeneration. 5. Local administration of M-Sch after TON also promote retinal ganglion cell survival. From the first year study, we have shown that systemic administration of MSC can significantly protect retinal ganglion cells after TON. Future study is under way to study combined local (M-Sch) and systemic MSC to promote RGC survival and axons regeneration; the mechanism of action of MSC in neuroprotection.

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INTRODUCTION

Traumatic optical neuropathy (TON) results from trauma to optic nerve by head and eye injuries to both military and civilian population such as accidents, and blast related combat trauma [1-3]. In a military report, 82% of severe eye injuries were caused by blast and blast fragmentation. TON leads to irreversible blindness and represent a major public health burden with both economical and social impacts. Unfortunately, treatment is still rather limited. Cytokine-mediated neuroprotection has been repeatedly demonstrated, and reliably reproduced, in multiple animal models with a range of optic nerve injury conditions [4-6] and block neuronal cell death in an excitotoxicity animal model [7-9]. A significant challenge to clinical implementation of this work is that cytokines are rapidly degraded by endogenous proteases. So the effect is short lasting. A direct and reliable approach to stem cell-mediated neuroprotection is a rational approach. A large body of evidence indicates that TON affects optic nerve and its target neurons in the central nervous system, which provide vital retrograde trophic support to optic nerve [10-12]. As an alternative approach, we propose a **non-invasive, systemic delivery of stem cells to optic nerve and related target neurons in the brain**. The systemic administration of stem cells offers substantial advantages over local delivery. These cells can exert therapeutic effects over the injured optic nerve and its targeted neurons in the brain, and multiple injections can be performed if needed. Others have successfully used the intravenous administration of MSC for treating stroke, cerebral ischemia, brain injury and myocardial infarction [13-15]. Based on the extensive experience with both MSC and M-Sch as therapies for regenerative and degenerative medicine, this study will determine whether it is realistic to transfer this treatment to the clinical setting.

BODY

Animal models: Long Evan rats are used in the first year study. Traumatic axonal injury (TAI) model was first created with a 60-g Yasargil aneurysm clip (Aesculap AG &C0, Tutlingen, Germany, arrow in image A) according to published protocol (16). However, we found it is impossible to use the Yasargil aneurysm clip, since it cannot perform 'dissecting', which is critical for free blood vessels from optic nerve bundle. We made a special clip by modifying a fine forceps (see image B). A reliable TAI model is created by using this modified forceps.
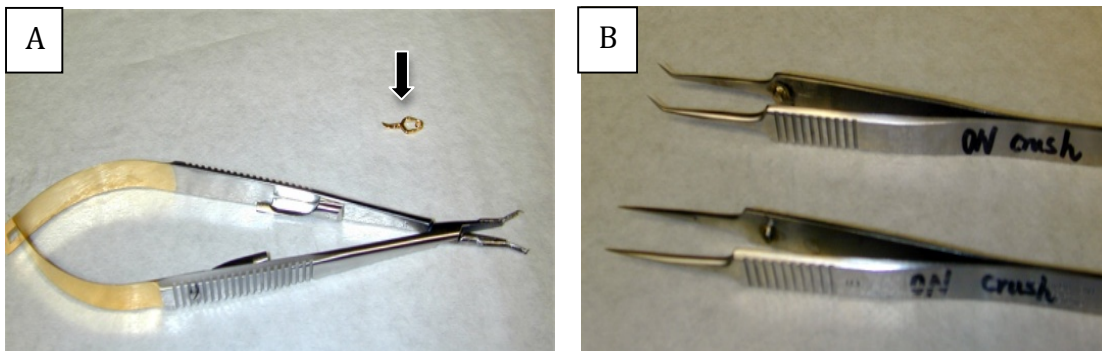
2. Isolation rat bone marrow derived mesenchymal stem cells (MSC, see image A); induction of Schwann cells from MSC (M-Sch, see image B) and MSC were purified with BD IMagnet combine with FACS analysis.

Isolation MSC from Long Evans rats using our published protocols (17), Image A showed MSC at passage O.
Induction of Schwann cells from MSC according to published protocol (18-19). Image B showed antibody against S100 staining of Schwann cells induced from MSC. Graph C showed FACS analysis after CD54/CD90 selection.

A

B

C

unstained | IgG2a | IgG1

CD45 | CD54 | CD90
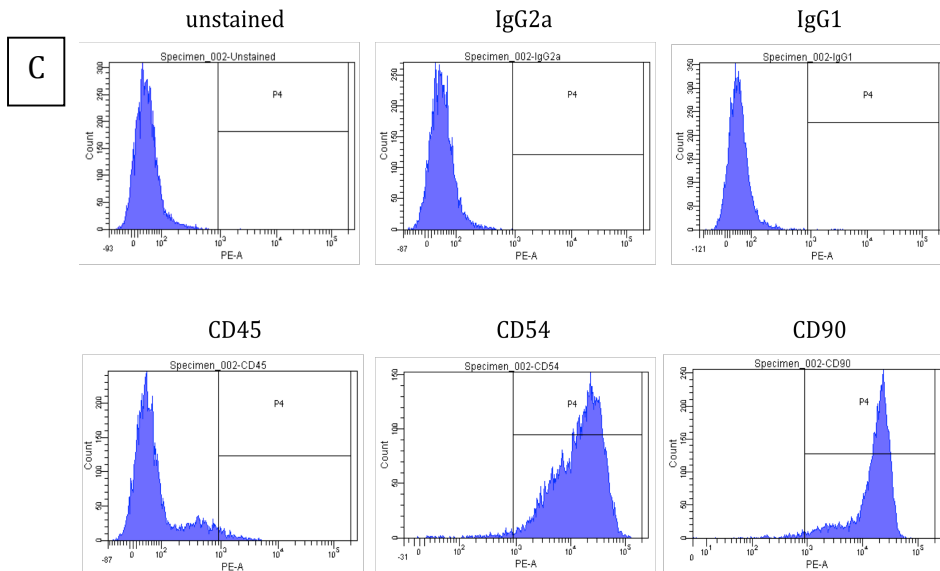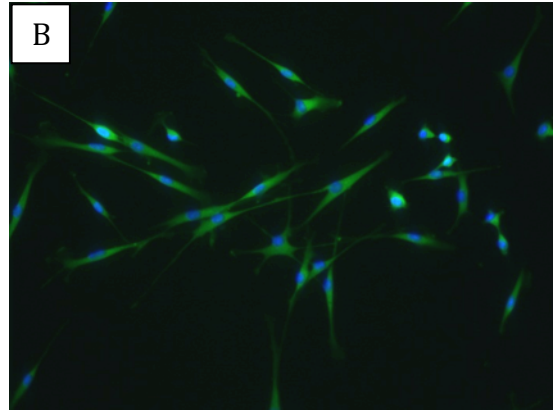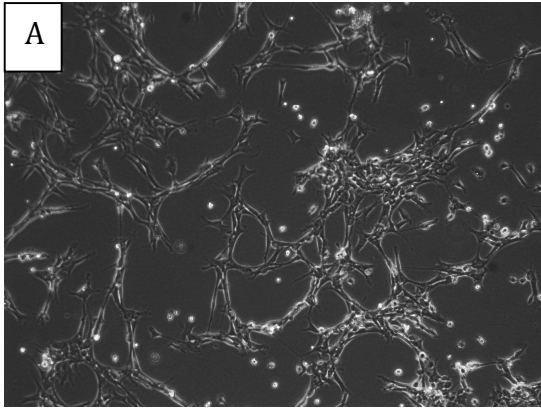
3. Work out protocols for creating TAI with our customized forceps; cholera toxin B (CTB) to anterogradely labeling optic nerves and fluorogold to the superior colliculus to retrogradely label retinal ganglion cells.

A
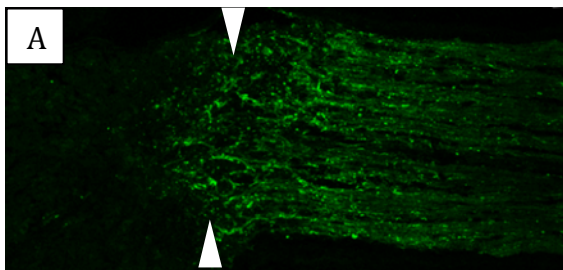
Optic nerve crush with our customized forceps. Image A is the image with CTB injection into vitreous cavity to anterogradely label optic nerves (green) after optic nerve crush (triangles showed nerve crush site).

6
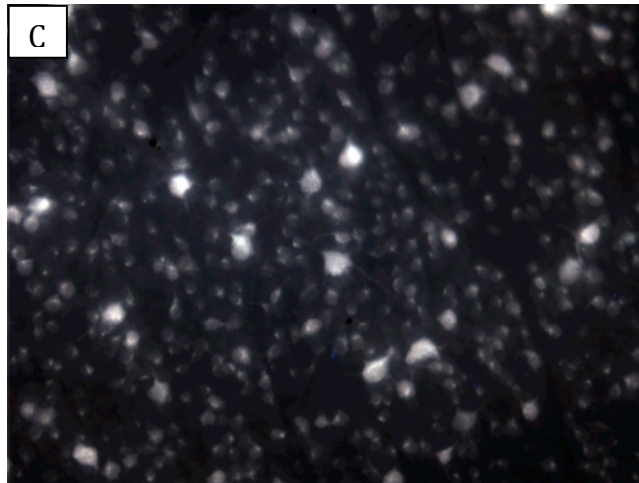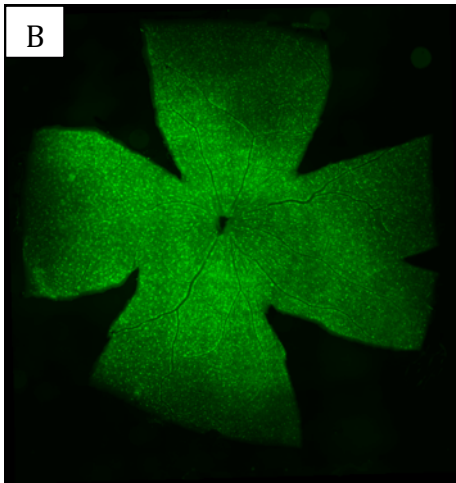
Retrogradely labeling retinal ganglion cells by applying fluorogold to the superior colliculus. Image B is the retinal whole mount showing fluorogold labeled retinal ganglion cells; Image C is high power image of fluorogold labeled retinal ganglion cells.

4. **Cell count with Zeiss stereology**

Stereology (Optical Fractionator) was used as described previously (20) to count the number of RGC in all conditions to minimize bias and optimize reliability. Using an Axioskop 2 MOT Zeiss microscope with a x2.5 objective lens (Zeiss, Germany), a semiautomatic stereology system (StereoInvestigator, Microbrightfield) was used to trace the area of interest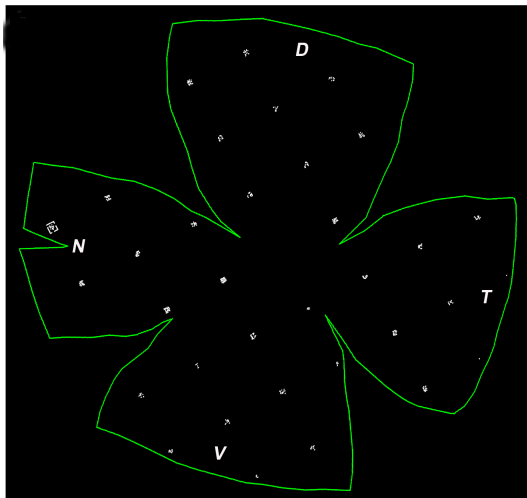, and a x40 magnification (Leitz) was used to count the number of RGC. For each section the computer randomly placed a 100 µm by 100 µm counting frame in different areas of the whole retina (1200 µm X 1200 µm in "Fractioner") with a number of average sampling sites of 30-40. Cells that were within the counting frame or touching the green line were counted and marked with a cross. The optical fractionator estimated the total number of RGCs by relating the number counted in the random counting frames to the sectional volume and then multiplying it by the reference volume.
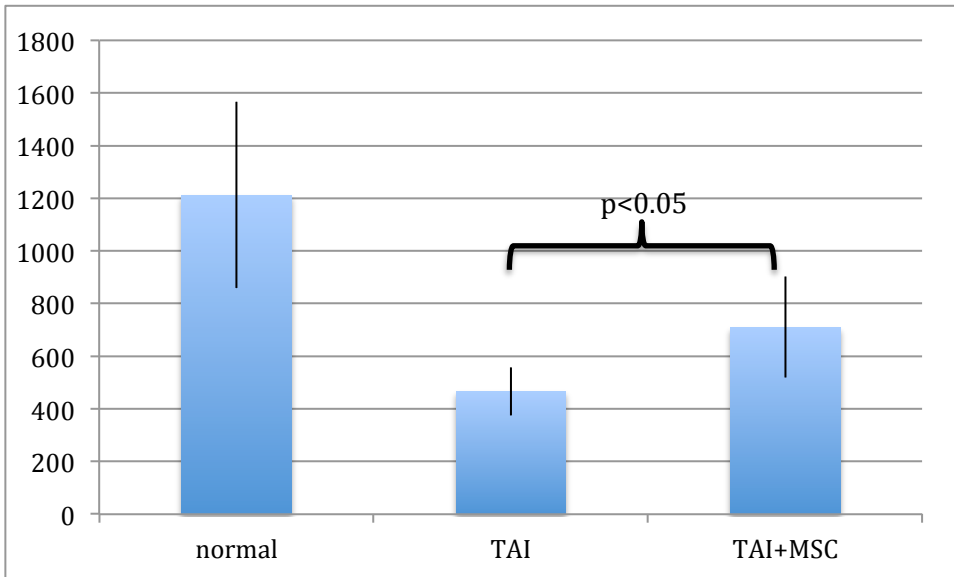
This graph showed RGC survival at 8days after TAI with intravenous injection of MSC, about 60% RGC survived compared to untreated control; while TAI without treatment, 40% RGC survived. The difference between MSC treated and untreated control is significant ($p<0.05$).

Data are presented as mean± standard deviation and analyzed with GraphPad Prism 5.01 for Windows (GraphPad software Inc). Statistical analyses were made using analysis of variance (ANOVA) and Newman-Keuls multiple comparison test. Differences were considered to be significant at $p < 0.05$.
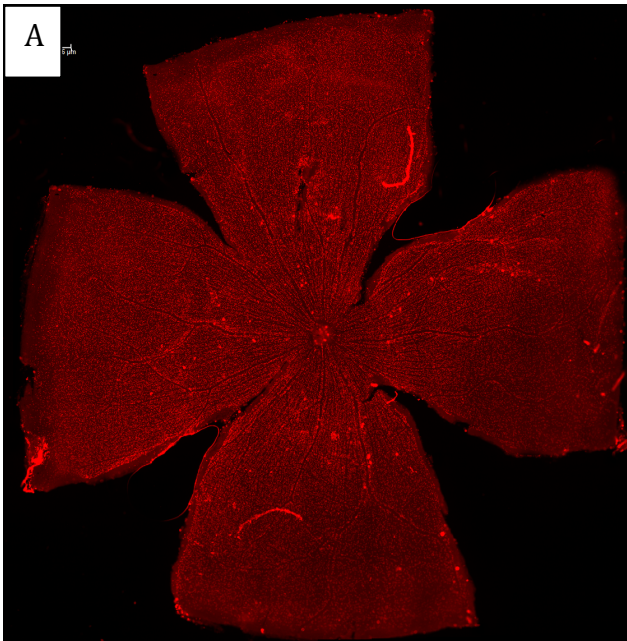
8 days after optic nerve crush and intravenous injection of one million MSC. Image A showed retinal whole mount with RGC antibody-Brn3 staining showing overall protection of RGC after intravenous injection of MSC 24hours following TAI.
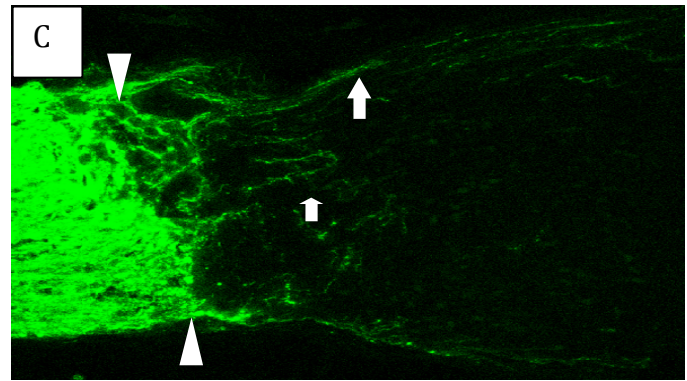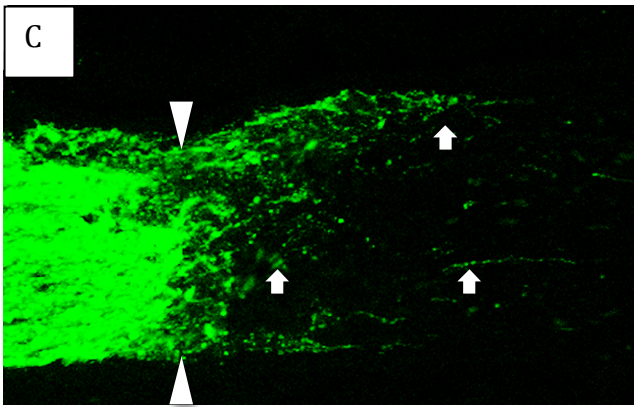
Image B&C: optic nerve section with CTB antrogradely labeled optic nerve axons showing regeneration of RGC axons (arrows) after intravenous injection of MSC 24hours following optic nerve crush (triangles showed crush sites).

5. Functional evaluation

A. Optokinetic responses (OKR).
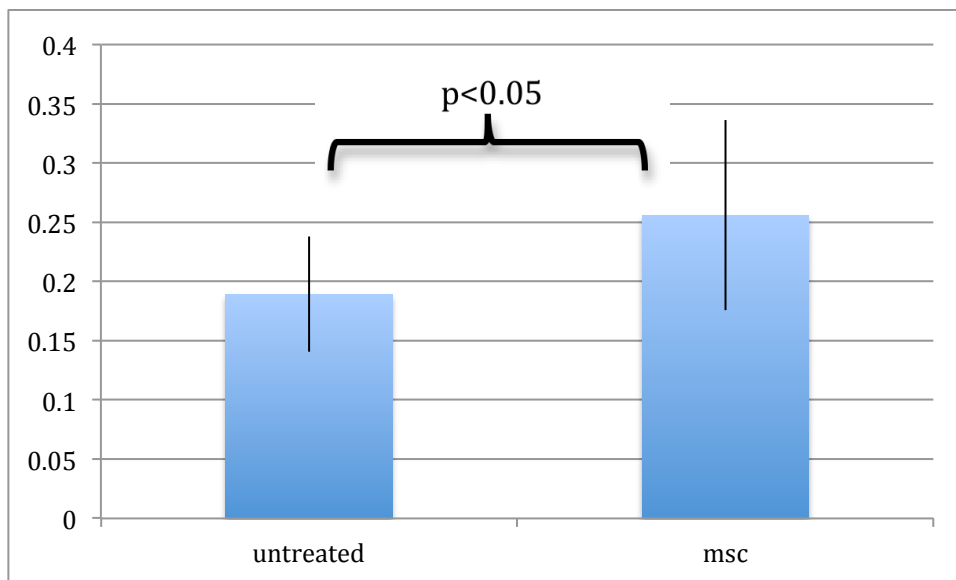
Using our established protocol, animals with TAI at one week had visual acuity reduced to about 0.2 cycle/degree (c/d); while intravenous administration of MSC preserved visual acuity. However, the visual acuity is still reduced to more than 50% of the normal level (>0.5c/d).

B: Electroretinogram (ERG) ERG measure full-field retinal potential from the cornea. Under scotopic conditions, a-wave is generated by photoreceptor phototransduction; b-wave is mainly generated by depolarization of ON-bipolar cells and Müller cells. The Scotopic threshold responses (STR) are created from the innermost retina, where the RGC bodies are located.

Our preliminary study showed that at one week after ONC without treatment, both a-and b-waves reduced compared with untreated wild type rats. Further study will measure STR, which is a good measurement to test retinal ganglion cells after TAI.

C. Luminance threshold recording (LTR) from the superior colliculus

The functional state of the retina was evaluated by recording the multi-neuronal responses in multiple (16–18) microelectrode penetrations into the unilateral superior colliculus (SC) of anesthetized rats. At each recording site, the receptive field was located by presenting flashes of the light spot of 3° in diameter. Response luminance threshold was then measured and defined as a minimal luminance of the stimulating light spot eliciting criterion multi-unit response (of amplitude twice of the level of the background activity). This procedure results in a map of focal luminance thresholds over the whole visual field of the eye contralateral to the tested SC. Based on these recordings, the cumulative curve of the luminance thresholds across the retina was calculated, which showed the percent of retinal area (y-axis) where the visual thresholds were less than the values indicated at the x-axis. Our LTR showed that there was no signal recorded after optic nerve crush, indicating the integrity of retina is needed for luminance threshold recording.

6. Issues and future study

• Enhance retinal ganglion cell survival by manipulating MSC specific homing

• Promote retinal ganglion axon regeneration by combining local and systemic intervention

• Combine retinoid acid with MSC to promote retinal ganglion survival and axon regeneration (need to get approval from the Army Contracting Officer Representative)

• Target on one and two week time points after TAI to get maximum retinal ganglion cell   protection and axon regeneration

• Repeat systemic administration of MSC to see long-term efficacy

• Continue to work on rat model for TAI, prelabel MSC for tracking their distribution and fate

• Study the mechanism of action of MSC in retinal ganglion cell protection; identify factors that protect retinal ganglion after TAI, then transfect the factor(s) to MSC to enhance its neuroprotection.

KEY RESEARCH ACCOMPLISHMENTS

- Reliable create TAI rat model by using our modified forceps
- Reliable isolate rat MSC and induction of Schwann cells from MSC (M-Sch)
- Worked out a new protocol for MSC purification with BD IMagent combine FACS analysis
- Reliable anterogradely label retinal ganglion cells and axons by injecting CTB into vitreous cavity; prepare for retinal whole mount
- Reliable retrogradely label retinal ganglion cells by applying fluorogold onto the superior colliculus
- Worked out protocol for quantifying retinal ganglion cells on retinal whole mount preparation
- Intravenous administration of MSC protect retinal ganglion cells after TAI and promote axons regeneration
- Applying M-Sch to optic nerve crush site preserve retinal ganglion cells after TAI
- The Scotopic threshold responses (STR) are the better measurement for TAI model
- Optokinetic response provides non-invasive measurement for TAI model

- Luminance threshold recordings from the superior colliculus are not suitable for evaluating retinal function after TAI

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- The research will be presented at ARVO, 2014, Orlando, FL.

- Optic nerve crush model can be reliably created by using our modified forceps.
- MSC can be purified by BD IMagnet combine with FACS analysis
- Post-doc fellowship will be applied by the end of October; We also get ready to apply grant from California Institute Regenerative Medicine (CIRM) based on work supported by this award

- **CONCLUSION:** We have reliably created rat model for TAI; reliably isolated MSC and induction of Schwann cells. We have found that non-invasive administration of MSC can protect retinal ganglion cells after TAI and local administration Schwann cells derived from MSC also protect retina ganglion cells. Systemic administration of MSC promotes axon regeneration, however axon regrowth is rather limited. To evaluate retinal function after TAI and intervention, the scotopic threshold responses (STR) are the better measurement for TAI model; Optokinetic response also provides valuable indication of retinal function; and luminance threshold recording for the superior colliculus fails to record any retinal activities after TAI. Future study: long-term evaluation of retinal ganglion cell protection and axon regeneration after intervention; new regents that have approved to promote axon regeneration combine with systemic administration of MSC; prelabel MSC to track their distribution and fate and mechanism of action of MSC in neuroprotection and identify factors that protect retinal ganglion cells and promote axon regeneration.

REFERENCES

1.   Steinsapir, K.D. and R.A. Goldberg, *Traumatic optic neuropathy.* Surv Ophthalmol, 1994. **38**(6): p. 487-518.
2.   Steinsapir, K.D. and R.A. Goldberg, *Traumatic optic neuropathy: an evolving understanding.* Am J Ophthalmol, 2011. **151**(6): p. 928-933 e2.
3.   Sarkies, N., *Traumatic optic neuropathy.* Eye (Lond), 2004. **18**(11): p. 1122-5.
4.   Castillo, B., Jr., et al., *Retinal ganglion cell survival is promoted by genetically modified astrocytes designed to secrete brain-derived neurotrophic factor (BDNF).* Brain Res, 1994. **647**(1): p. 30-6.
5.   Klocker, N., et al., *In vivo neurotrophic effects of GDNF on axotomized retinal ganglion cells.* Neuroreport, 1997. **8**(16): p. 3439-42.
6.   Mey, J. and S. Thanos, *Intravitreal injections of neurotrophic factors support the survival of axotomized retinal ganglion cells in adult rats in vivo.* Brain Res, 1993. **602**(2): p. 304-17.
7.   Kido, N., et al., *Neuroprotective effects of brain-derived neurotrophic factor in eyes with NMDA-induced neuronal death.* Brain Res, 2000. **884**(1--2): p. 59-67.
8.   Kurokawa, T., et al., *BDNF diminishes caspase-2 but not c-Jun immunoreactivity of neurons in retinal ganglion cell layer after transient ischemia.* Invest Ophthalmol Vis Sci, 1999. **40**(12): p. 3006-11.
9.   Unoki, K. and M.M. LaVail, *Protection of the rat retina from ischemic injury by brain-derived neurotrophic factor, ciliary neurotrophic factor, and basic fibroblast growth factor.* Invest Ophthalmol Vis Sci, 1994. **35**(3): p. 907-15.
10.   Yip, H.K. and K.F. So, *Axonal regeneration of retinal ganglion cells: effect of trophic factors.* Prog Retin Eye Res, 2000. **19**(5): p. 559-75.
11.   Isenmann, S., et al., *Short communication: protection of axotomized retinal ganglion cells by adenovirally delivered BDNF in vivo.* Eur J Neurosci, 1998. **10**(8): p. 2751-6.
12.   Chen, H. and A.J. Weber, *BDNF enhances retinal ganglion cell survival in cats with optic nerve damage.* Invest Ophthalmol Vis Sci, 2001. **42**(5): p. 966-74.
13.   Nagaya, N., et al., *Intravenous administration of mesenchymal stem cells improves cardiac function in rats with acute myocardial infarction through angiogenesis and myogenesis.* Am J Physiol Heart Circ Physiol, 2004. **287**(6): p. H2670-6.
14.   Savitz, S.I., et al., *Intravenous autologous bone marrow mononuclear cells for ischemic stroke.* Ann Neurol, 2011. **70**(1): p. 59-69.
15.   Chen, J., et al., *Intravenous administration of human bone marrow stromal cells induces angiogenesis in the ischemic boundary zone after stroke in rats.* Circ Res, 2003. **92**(6): p. 692-9.
16.   Kawaguchi, I., et al., *In vivo imaging and quantitative evaluation of the rat retinal nerve fiber layer using scanning laser ophthalmoscopy.* Invest Ophthalmol Vis Sci, 2006. **47**(7): p. 2911-6.
17.   Wang, S., et al., *Non-invasive stem cell therapy in a rat model for retinal degeneration and vascular pathology.* PLoS One, 2010. **5**(2): p. e9200.
18.   Dezawa, M., et al., *Specific induction of neuronal cells from bone marrow stromal cells and application for autologous transplantation.* J Clin Invest, 2004. **113**(12): p. 1701-10.
19.   Park, H.W., et al., *Human mesenchymal stem cell-derived Schwann cell-like cells exhibit neurotrophic effects, via distinct growth factor production, in a model of spinal cord injury.* Glia, 2010. **58**(9): p. 1118-32.
20.   Hassani Z, O'Reilly J, Pearse Y, Stroemer P, Tang E, Sinden J, Price J, Thuret S. Human neural progenitor cell engraftment increases neurogenesis and microglial recruitment in the brain of rats with stroke. PLoS One. 2012;7(11):e50444.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Shaomei Wang	POSITION TITLE Associate Professor
eRA COMMONS USER NAME Wangsha	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education,*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Jinzhou Medical College, PR China	B.M. (M.D)	1984	Medicine
Chinese Medical University, PR China	Masters	1987	Neuroscience
University of Sheffield, UK			
Institute of Ophthalmology, UCL, London	Ph.D. Post-doc	1997 2001	Visual neuroscience Cell-based therapy

A. Personal Statement

Our laboratory has a long history of applying cell-based therapy for retinal degeneration. We have explored the efficacy of a range of different cell types (i) cells to replace defective retinal pigment epithelial (RPE) cells such as human embryonic stem cell derived –RPE cells, (ii) cells that appear to function by releasing growth factors such as peripheral nerve ensheathing cells (Schwann cells) or cells genetically modified to release growth factors and (iv) cells with multiple functions such as stem cells and progenitors. Our studies have provided the pre clinical data for three prominent first in man human clinical trials for retinal degeneration using either human embryonic stem cells (Advanced Cellular Therapeutics) or adult mesenchymal stem cells (Johnson and Johnson) or central nervous system derived neural stem cells (StemCell inc) . Recently, my laboratory has pioneered a new approach to treatment involving systemic administration of mesenchymal stem cells and shown extensive morphological and functional preservation in rodent models of retinal disease. I was recent recruited to the Cedars-Sinai Regenerative Medicine Institute where we will be collaborating with the director, Dr Clive Svendsen who has a long history of using stem cells to model and treat diseases of the CNS, other senior faculty conducting research into the eye, and immunologists with an interest in transplantation. I will continue to work with our long-term collaborators Dr Gamm (U of Wisconsin) using retinal progenitors/stem cells to limit retinal degeneration. Our preclinical studies will be focused on the efficacy, long-term survival of donor cells, mechanism of action and immunological responses after cell-based therapy. The object of our translational research program is to treat retinal degeneration and optic nerve repair with cellular therapy.

B. Positions and Honors.

Positions and Employment

2012-prosent   Associate professor, Cedars-Sinai Regenerative Medicine Institute, LA, CA

2011-2012   Research Scientist, Cedars-Sinai Regenerative Medicine Institute, LA, CA
2006 - 2011   Assistant Professor, Casey Eye Institute, OHSU, Portland, USA

2005- 2006   Assistant Professor, Moran Eye Center, Utah, USA
2001 - 2005   Senior lab specialists, Institute of Ophthalmology, UK
1997 - 2001   Post-doctoral fellow, Institute of Ophthalmology, UK
1994 - 1997   PhD student, University of Sheffield, UK.
1991 - 1993   Visiting Scholar, University of Sheffield (supported by British Council).
1987 – 1991   Lecturer, JinZhou Medical College, PR China.

Honors
1984-1987   Graduate studentship, Jinzhou Medical college, PR China
1991-92   British Council and Chinese government award (visiting scholar to University of
                          Sheffield, UK)
1992   Overseas Research scholarship
 2004   Permanent US residency awarded in the US National Interest on the basis of
Outstanding
                         Researcher
 2010   Paper was selected as Paper of the Month (March) at OHSU med school.

Other Experience and Professional Memberships

 Association for Research in Vision and Ophthalmology
 Society for Neuroscience
 Editorial member of Transplantation & technology and research
 Investigative Ophthalmology and Visual Science
 Experimental Eye Research
 Vision Research
 Current Eye Research
 Expert Reviews
 Stem cells international

B. Selected peer-reviewed publications

Wang S, and Redgrave P. (1997) Microinjections of muscimol into lateral superior colliculus disrupt orienting and oral movements in the formalin model of pain. Neuroscience 81: 967-988.

Kwan A, Wang S, Lund RD. (1999) Reconstruction of photoreceptor layer in rodent model. Exp Neurol 159 (1): 21-33.

Wang S, Villegas-Perez MP, Vidal-Sanz M, Lund RD. (2000) Vascular consequence of the photoreceptor loss in the rd mouse and the effects on retinal ganglion cell axons. Invest Ophthal Vis Sci. 41:537-545.

Coffey PJ, Girman SV, Wang S, Keegan DJ, Adamson P, Greenwood J, Lund RD. (2002) Long-term preservation of cortically mediated visual function in dystrophic RCS rats by transplantation of immortalised retinal pigment epithelial cells. Nature Neuroscience. 5:53-56.

Wang S, Lu B, Wood P, Lund R. (2005) Grafting of ARPE-19 and Schwann cells to the subretinal space in RCS rats. Invest Ophhalmol Vis Res. 46: 2552-2560, 2005.

Wang S, Lu B, Lund R. (2005) Morphological Changes in the RCS Retina during Photoreceptor

Degeneration and after Cell-based Therapy. J Comp Neurol. 491(4): 400-417.

Raymond D. Lund and Shaomei Wang (2006). Cell-Based Therapies to Restrict the Progress of Photoreceptor Degeneration. Book: Retinal Degenerations, editors: Tombran-Tink and Barnstable. 620-2; Humana Press; Chapter 17: 317-342.

Gamm DM, Wang S, Lu B, Girman S, Holmes T, Bischoff N, Shearer RL, Sauve Y, Capowski E, Svendsen CN, Lund RD. Protection of visual functions by human neural progenitors in a rat model of retinal disease. PLoS ONE. 2007 Mar 28;2:e338.

Wang S, Lu B, Girman S, Holmes T, Bischoff N, Lund RD. Morphological and functional rescue in RCS rats after RPE cell line transplantation at a later stage of degeneration. Invest Ophthalmol Vis Sci. 2008 Jan;49 (1):416-21.

Wang S, Girman S, Lu B, Bischoff N, Holmes T, Shearer R, Wright L, Svendsen CV, Gamm DM, R Lund. Long Term Vision Rescue by Human Neural Progenitors in Rat Model of Photoreceptor Degeneration. Invest Ophthalmol Vis Sci. 2008 July; 49 (7): 3201-6.

Francis* PJ, Wang* S, Zhang Y, Brown A,Hwang T, McFarland T, Jeffrey, B.G, Lu B, Wright, L, Appukuttan B, Wilson, D.J,Stout, J.T, Neuringer M, Gamm* DM, Lund* RD. subretinal Transplantation of forebrain Progenitor Cells in Non-human Primates: Survival and Intact Retinal function. Invest Ophthalmol Vis Sci. 2009;50 (7): 3425-31.

Bin Lu*, Christopher Malcuit*, Shaomei Wang*, Sergej Girman, Peter Francis, Linda Lemieux, Robert Lanza, Raymond Lund. Long-term Safety and Function of RPE from Human Embryonic Stem Cells in Preclinical Models of Macular Degeneration. Stem Cells. 2009:27 (9): 2126-35.

Lu B, Wang S, Francis PJ, Li T, Gamm DM, Capowski EE and RD Lund. Cell Transplantation to Arrest Early Changes in an USH 2A Animal Model. Invest Ophthalmol Vis Sci. 2009 Dec.3 (ePub).

Wang S*, Lu B, Girman S, Duan J, McFarland T, Zhang QS, Grompe M, Adamus G, Appukuttan B and R Lund. Non-invasive stem cell therapy in a rat model for retinal degeneration and vascular pathology. PLoS ONE 5(2):e9200.
Lu B, S Wang*, S. Girman, T McGill, V Ragaglia, R Lund. Human adult bone marrow-derived somatic cells rescue vision in a rodent model of retinal degeneration. Exp Eye Res. 2010 :91 (3): 449-55.

Trevor J. McGill, Benjamin Cottam, Bin Lu, Shaomei Wang, Sergej. Girman, Alexandra Capela, Stephen L. Huhn, Ray D. Lund. Transplantation of human central nervous system stem cells: Neuroprotection in retinal degeneration. Euro J Neurosci 2012:35: 468-77.

Adamus Grazyna, Wang Shaomei, Kyger Madision, Worley Aneta, Lu Bin and Burrows Greg. Systemic immunotherapy delays photoreceptor cell loss and prevents vascular pathology in RCS rats. Molecular vision. 2012.
Jonathan G. Swoboda, Jimmy Elliott, Vishal Deshmukh, Lorenzo de Lichtervelde, Weijun Shen, Matthew S. Tremblay, Charles Y. Cho, Bin Lu, Sergej Girman, Shaomei Wang, Peter G. Schultz. Small molecule mediated proliferation of primary retinal pigment epithelial cells. ACS Chem Biol. 2013, May8
Nicolás Cuenca[1], Laura Fernández-Sánchez[1], Trevor J. McGill[2], Bin Lu[3], Shaomei Wang[3], Raymond Lund[4], Stephen Huhn[5], Alexandra Capela. Phagocytosis of photoreceptor outer segments by transplanted human neural stem cells as a neuroprotective mechanism in retinal degeneration. Invest Ophthalmol Vis Sci. 2013, Sep 17.
Bin Lu, Catherine W Morgans, Sergey Girman, Raymond Lund and Shaomei Wang Retinal Morphological and Functional Changes in an Animal Model of Retinitis Pigmentosa. Vis Neurosci, 2013: 1-13.
Bin Lu, Catherine W. Morgans, Sergey Girman, Jing Luo, Jiagang Zhao, Hongjun Du, SiokLam Lim, Sheng Ding, Clive Svendsen, Kang Zhang and Shaomei Wang. Neural Stem Cells Derived by Small

Molecules Preserve Vision. Transl Vis Sci Technol. 2013: 2.

C. Current Grant Support

<u>1RO1EY020488</u>   Wang (PI)
         09/01/2011-08/31/2016
NIH/NEI
Development of non-invasive cell-based therapy for retinal degeneration and associated vascular pathology.
The overall objective of this research proposal is to preserve vision and limit vascular pathology using non-invasive MSC therapy in rodent models for retinal degeneration. The MSCs have been widely used in both regenerative and degenerative medicine. The proposed research will be critical in determining whether systemic administration of MSCs offers a realistic likelihood of translation to the clinic for the treatment of retinal degeneration and ocular vascular pathology.
Role: PI

CS-RMI (start-up fund)   Wang (PI)
06/01/2011-05/31/2015
Applying stem cell therapy for retinal degenerative disease

<u>FFB Wynn-Gund</u>   Gamm (PI)
06/01/08-05/31/13

Customized IPS cell therapy for recessive monogenetic retinal degenerative disease.
The objective of this grant is to examine the efficacy of IPS cells derived from recessive monogenetic retinal degenerative disease in rodent models. Our module will provide fundamental information regarding how these IPS cells behave in the degenerative retina.
Role: subcontract-PI

Department of Defense   Wang (PI)   09/01/12-08/31/14
Non-invasive cell based therapy for traumatic optic neuropathy

Janssen Research & development, LLC   Wang (PI)   08/01/12-07/31/14
Preclinical research with umbilical derived stem cell therapy for RCS rodent model for retinal degeneration.

<u>Pending</u>

NIH (R01)   Meyer (PI)
Modeling glaucoma with patient-specific human induced pluripotent stem cells
Role: Co-Investigator
SUPPORTING DATA: All figures are embedded in the report.